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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/082,046	02/20/2002	Jim Wells	SUNESIS.2DV1C2	9481

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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 06/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/082,046	WELLS ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40,41,43,47,59 and 64-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-41, 43, 47, 59 and 64-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The Response filed March 9, 2004 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

3. Claims 40-41, 43, 45-50, 59-60 and 64 were pending. Applicants added claims 65-67and canceled claims 45-46, 48-50 and 60. Furthermore, Applicants amended claims 40, 47, 59 and 64. Therefore, claims 40-41, 43, 47, 59, 64-67 are currently pending and examined on the merits. The Examiner notes that claim 64 is mistakenly listed as "Previously presented" instead of as "Currently amended" (e.g., see 3/9/2004 response, page 3 of claims). Confirmation of the correct status of claim 64 is respectfully requested.

Withdrawn Objections/Rejections

4. The objections to claims 45-46 are hereby withdrawn in view of Applicants' amendments. The New Matter rejection under 35 U.S.C. 112, first paragraph is hereby withdrawn in view of Applicants' amendments and/or arguments. With respect to the rejections under the second paragraph of 35 U.S.C. 112, the rejections denoted A-C are withdrawn in view of applicant's amendments to the claims and/or cancellation of claims. The Kim et al. rejection

under 35 U.S.C. 102(a) is hereby withdrawn in view of Applicants' amendments and/or arguments. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC § 103

5. Claims 40-41, 43, 47, 59, 64-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. (WO 98/11436) (Date of Patent is **March 19, 1998**) (see IDS, Paper No. 2, entry 9) and Siuzdak (Siuzdak, G. Mass Spectrometry for Biotechnology. New York: Academic Press. **1996**, pages 119-126).

For ***claims 40-41, 43, 59 and 64-67***, Kim et al. (see entire document) disclose a screening method for "identifying" ligands that do not have a high affinity for a target macromolecule (which is typically a protein) using combinatorial "tethering" techniques (e.g., see Kim et al., page 1, paragraph 1; see also page 2, paragraphs 1-2), which reads on claims 40-41, 43, 59 and 64-67. For example, Kim et al. teach obtaining a target protein comprising an -SH group, masked -SH group, or activated -SH group (e.g., see Kim et al., claims 1-2, "target molecule, as obtained or as modified, contains one member of a binding pair ... wherein the binding partner and the reactive moiety are each a free sulfhydryl group [i.e., an –SH group] or a sulfur moiety which is available for disulfide bond formation through exchange"; see also page 3, paragraphs 2-3; see also page 27, lines 15-26 wherein cysteine sulfhydryl groups are used). Kim et al. also teach combining said target protein with a library simultaneously containing at least two non-

oligomeric ligand candidates wherein said ligand candidates each comprise a disulfide bond, and wherein said ligand candidates each are less than about 2000 daltons in size under disulfide exchange conditions, in the presence of a reducing agent (e.g., see Kim et al., see also page 11, paragraph 2, "As obtained, a target molecule might also include a binding partner (such as a sulfur moiety within a cysteine residue) which is available or can be made available (e.g., as a free sulfhydryl group or sulfur that is available for disulfide bond formation through exchange) for binding with a reactive moiety. If such a target molecule is used potential ligands [i.e., at least 2] can be modified to include a free sulfhydryl group or a sulfur that is available for disulfide bond formation through exchange ... Here, non-specific binding of target molecule and potential ligands occurs through formation of a disulfide bond"; see also page 17, paragraph 1 disclosing the use of reducing agents, "non-specific interaction (here, disulfide bond formation) can be varied by adjusting the concentration of external ... reducing agents ... for example ... glutathione"). Kim et al. does not explicitly state that the ligands are "less than about 2000 daltons in size" or "less than 750 daltons", but Kim et al. disclose ligands selected from the group consisting of "small organic molecules, pharmaceuticals, toxins" (see Kim et al., page 21, lines 15-20; see also claim 3 further disclosing steroids, hormones, caffeine, ATP, cyclosporin, cyclophilin), which would encompass molecules that are less than 750 daltons in size. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the

burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Furthermore, Kim et al. disclose the formation of a target protein-ligand conjugate (e.g., see Kim et al., claims 1-2; see also page 3, paragraphs 2-3; see also page 9, line 14; see also page 14, paragraph 1; see also page 28, paragraph 1, "This experiment illustrates under conditions wherein a specific interaction between a target molecule and ligand can take place, preferential formation of disulfide-mediated ligand-target heterodimers [i.e., a target protein-ligand conjugate] can be observed"). In addition, Kim et al. also disclose that the target-ligand conjugate can be separated from the mixture (e.g., see Kim et al., page 3, lines 24-26, "Optionally, the complex of the ligand specifically bound to the target molecule can be separated or removed from the library or collection"). Finally, Kim et al. also disclose determining the identity of the non-oligomeric ligand present in said target protein-ligand conjugate (e.g., see Kim et al., abstract, "Non-specific affinity enhancement as a method of identifying and detecting members, such as ligands ... in a collection or library of potential ligands"; see also Summary of the Invention; see also page 8, lines 18-20).

The prior art teachings of Kim et al. differ from the claimed invention as follows:

For ***claims 40, 59 and 64***, the Kim et al. reference is deficient in that it does not specifically teach "subjecting said conjugate directly, without prior fragmentation and without liberation of the ligand from said conjugate, to mass spectrometry analysis" (e.g., see newly amended claims 40 and 59 in 3/9/2004 Response).

For **claims 47**, the Kim et al. reference is deficient in that although it teaches the use of reducing agents it does not explicitly mention the use of 2-mercaptoethanol.

However, Siuzdak teaches the following limitations that are deficient in Kim et al:

For ***claim 40, 59 and 64***, Siuzdak (see entire document) teaches the use of electrospray mass spectrometry to study both "non-covalent" and "covalent" antibody-antigen interactions including fragmentation techniques like MS^2 and MS^3 (see pages 119-126, especially figures 6.3-6.6 and Table 6.1). In addition, Siuzdak teaches subjecting conjugates "directly, without prior fragmentation and without liberation of the ligand for said conjugate, to mass spectrometry analysis" (e.g., see Siuzdak, page 123, Figure 6.3 wherein the peak at 26,769 represents the parent ion for a "antibody/hapten complex" that has not been fragmented or dissociated before being subjected to mass spectrometry analysis).

For ***claim 47***, the Examiner contends that any reducing agent commonly used would have been obvious including 2-mercaptoethanol because each would have the same effect and the final decision would ordinarily be determined on cost and commercial availability of the reagents.

It would have been obvious to one skilled in the art at the time the invention was made to "identify" target/ligand interactions using the method steps as taught by Kim et al. in conjunction with the mass spectrometer techniques as taught by Siuzdak because Siuzdak explicitly shows that the technique can be applied to both "covalent" and "non-covalent" interactions including "antibody-antigen" interactions (see Siuzdak, figures 6.3, 6.5; see especially paragraph bridging pages 125-126, "Electrospray mass spectrometry

has also demonstrated its potential in the analysis of non-covalent interactions between an antibody and a hapten, and for observing covalent protein-bound intermediates in an antibody-catalyzed reaction"), which would encompass the "antibody-antigen" complexes disclosed by Kim et al. (e.g., see Kim et al., page 4, lines 7-8 disclosing antibody-antigen reactions; see also lines 18-19 disclosing both "covalent" and "non-covalent" interactions). Furthermore, one of ordinary skill in the art would have been motivated to use the mass spectrometers as taught by Siuzdak with the antibody-antigen conjugates as taught by Kim et al. (or any other target-ligand interaction) because Siuzdak explicitly states that electrospray has "demonstrated its potential" for these systems (see Siuzdak, page 126, paragraph 1).

Furthermore, one of skill in the art would be especially motivated to use mass spectrometry as disclosed by Siuzdak with the "antibody-antigen" complexes as described by Kim et al. because Siuzdak discloses that BOTH "covalent" and "non-covalent" interactions can be measured (and distinguished) using a mass spectrometer (see Siuzdak, page 123, paragraph 3, "Declusterin potentials on the order of 70 V or greater usually promote the dissociation of noncovalent complexes as well as covalent fragmentation, while lower potentials (<70 V) are conducive to the observation of noncovalent complexes (protein complexes have been analyzed at declustering potentials of 40 V). In order for the method of Kim et al. to work the modified antibodies must bind "covalently" to their respective antigens (see Kim et al., figure 1 disclosing the covalent attachment of an antigen to a sulfhydryl group on the modified antibody). Therefore, any analytical technique that can confirm the "covalent" attachment of the

antigen to the modified antibody is particularly useful. Consequently, a person of skill in the art would be motivated to "identify" even a "known" ligand using a mass spectrometer to determine the type of interaction (i.e., covalent v. non-covalent) to ascertain whether the modified ligand is truly able to bind to its respective target via a "covalent" bond as required by the method. Consequently, a person of skill in the art would be motivated to search for the "modified" ligands and/or targets as disclosed by Kim et al. with electrospray mass spectroscopy as disclosed by Siuzdak to find modified ligands that can "covalently" bind to the targets as opposed to any unwanted "non-covalent" interactions that might occur.

Finally, one of ordinary skill in the art would have reasonably expected to be successful because Siuzdak shows many examples of target-ligand interactions that have successfully been analyzed on a mass spectrometer including antibody-antigen (e.g., see figures 6.3 and 6.5) and that both covalent and non-covalent interactions can be studied (e.g., see paragraph bridging pages 125-126).

Response

6. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "Siuzdak does not explicitly state that electrospray mass spectrometry has demonstrated its potential for identifying ligands present in a covalent

conjugate between a target protein and a ligand of the protein. The quoted sentence is limited to the observation of covalent-bound intermediates in an antibody-catalyzed reaction. Observing a chemical entity, such as a protein-bound intermediate, and determining the identity of such chemical entity are two very different things" (e.g., see 3/9/2004 Response, paragraph bridging pages 7-8).

[2] Applicants argue, "the combination [of references] would still not make obvious the invention as presently claimed. The claims require determination of the identity of a ligand present in a target protein-ligand conjugate 'by subjecting said conjugate directly, without prior fragmentation and without liberation of the ligand from said conjugate, to mass spectrometry analysis.' Such method is not disclosed or suggested by Siuzdak, therefore, its combination with Kim et al. does not make obvious the claims currently pending.

This is not found persuasive for the following reasons:

[1] In response to applicant's arguments against the Siuzdak reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, the "combination" of references teaches, "identifying" a ligand using mass spectrometry.

Furthermore, the Examiner notes that Applicants' assertions that Siuzdak is "limited to the observation covalent bound intermediates in an antibody-catalyzed reaction" and "[o]bserving a chemical entity, such as a protein-bound intermediate, and determining the identyiy of such chemical entity are two very different things" are wholly unsubstantiated (i.e., Applicants have not provided any scientific rationale that would support these statements). In

addition, the Examiner notes the Siuzdak teaches both "observing" and "identifying" covalent and non-covalent protein-ligand conjugates (e.g., see Siuzdak, page 123, figure 6.3 wherein the peak at 26,769 was "identified" as a single-chain catalytic antibody/hapten complex wherein the hapten is as shown in the figure).

In response to Applicants' argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the Examiner has provided ample motivation to combine the references (e.g., see newly amended rejection above, "one of ordinary skill in the art would have been motivated to use the mass spectrometers as taught by Siuzdak with the antibody-antigen conjugates as taught by Kim et al. (or any other target-ligand interaction) because Siuzdak explicitly states that electrospray has 'demonstrated its potential' for these systems (see Siuzdak, page 126, paragraph 1)". Furthermore, the Examiner notes that Applicants failed to address the motivation provided by the examiner in the second to last paragraph of the rejection (e.g., see newly amended rejection above, "one of skill in the art would be especially motivated to use mass spectrometry as disclosed by Siuzdak with the "antibody-antigen" complexes as described by Kim et al. because Siuzdak discloses that BOTH "covalent" and "non-covalent" interactions can be measured (and distinguished) ...").

[2] Again, in response to applicant's arguments against the Siuzdak reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, the "combination" of references teaches, "subjecting said conjugate directly, without prior fragmentation and without liberation of the ligand from said conjugate, to mass spectrometry analysis" (e.g., see newly amended rejection above). In addition, the Examiner notes that that Siuzdak alone also teaches applying mass spectroscopy to identify antibody/hapten complexes that have not been "fragmented" or "dissociated" (e.g., see Siuzdak, page 123, figure 6.3 showing a peak at 26,769 that represents a single-chain catalytic antibody/hapten complex that has not been "fragmented" or "dissociated").

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 272-0811.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
May 30, 2004

BENNETT CELSA
PRIMARY EXAMINER